Associations between several sites of cancer and twelve petroleum-derived liquids

Results from a case-referent study in Montreal

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SIEMIATYCKI J, DEWAR R, NADON L, GÉRIN M, RICHARDSON L, WACHOLDER S. Associations between several sites of cancer and twelve petroleum-derived liquids: Results from a case-referent study in Montreal. *Scand J Work Environ Health* 13 (1987) 493—504. A population-based case-referent study provided information on the associations between several types of cancer and 12 petroleum-derived liquids. All site-exposure combinations were investigated. The most interesting results concerned the following combinations: leaded gasoline-stomach cancer, aviation gasoline-kidney cancer (and the possible implications of this association for a similar effect of unleaded automotive gasoline), mineral spirits-squamous-cell cancer of the lung, diesel fuel-nonadenocarcinoma lung cancer, lubricating oils-squamous-cell lung cancer, cutting fluids-bladder cancer, other mineral oils-bladder cancer, mineral spirits-prostate cancer, diesel fuel-prostate cancer, and lubricating oils-prostate cancer.

Key terms: carcinogenesis, diesel, lung neoplasms, neoplasms, occupational diseases, oil, petroleum, prostate neoplasms, stomach neoplasms.

A large population-based case-referent monitoring study was carried out in Montreal. It focused on occupational exposures as potential risk factors (34, 35). About 20 sites of cancer were included in the study. For each patient, information was obtained concerning past exposure to about 300 substances. The overall analytical strategy was to analyze subsets of substances at a time to determine whether there seemed to be any remarkable cancer-exposure associations.

This report examines the associations between the cancers in our study and the following 12 petroleum-derived liquids: automotive gasoline, aviation gasoline, mineral spirits, kerosene, jet fuel, diesel fuel, heating oil, cutting fluids, hydraulic fluids, lubricating oils and greases, other mineral oils, and crude oil. These substances include some of the most common exposures in the 20th century industrial environment. Over the years, they have been used in a fairly well circumscribed set of occupations and industries, although their compositions have evolved over time. None of them is a pure compound; rather they are complex mixtures of tens or hundreds of hydrocarbons of various molecular weight, including both saturated and unsaturated aliphatics and ring compounds.

Subjects and methods

A full description of the fieldwork and analytical methods can be found in another article (35). A brief outline follows.

Interviews were carried out for 3 726 cancer patients (response rate 82 %) diagnosed in one of the 19 participating Montreal-area hospitals. These patients were men aged 35 to 70 years. Many sites of cancer were represented, the main ones being: esophagus (107 cases), stomach (250 cases), colon (364 cases), rectosigmoid (233 cases), rectum (190 cases), liver (50 cases), pancreas (117 cases), lung (857 cases), prostate (452 cases), bladder (486 cases), kidney (181 cases), melanoma of the skin (121 cases), Hodgkin's lymphoma (53 cases), and non-Hodgkin's lymphoma (206 cases). Furthermore, it was possible to subdivide the lung cancer series into the following four histological categories with sufficient numbers: oat cell (159 cases), squamous cell (359 cases), adenocarcinoma (162 cases), and other cell types (177 cases). The last group includes mainly giant cell, spindle cell, and carcinoma not otherwise specified.

Each of these groups constituted a case series which was investigated in relation to each of the petroleum-derived liquids. For each case series, a reference group was selected from among the other cancer patients interviewed. Thus each subject could serve as a case in one analysis and as a "referent" in others. The criteria

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for selecting "referents" among the other cancers and the numbers of referents thereby selected for each site have been presented in another article (35). (For example, lung cancer patients were not included as referents in any of the analyses).

The in-depth interview elicited a detailed job history of the subjects and information on potentially confounding covariables. A team of chemists and hygienists examined each completed questionnaire and translated each job into a list of potential exposures (15). They did this on a checklist which explicitly listed some 300 of the most common occupational exposures in Montreal. For each product thought to be present in each job, the chemists noted their confidence that the exposure actually occurred (possible, probable, definite), frequency of exposure during a normal workweek (< 5, 5—30, and > 30 %), and the level of concentration of the agent in the work environment (low, medium, high).

For each subject, the data set comprised semi-quantitative information on the degree of exposure and the number of years of exposure to each of several hundred occupational substances. For the purpose of the analyses, two indices of exposure to each substance were computed: one comprising the concentration, frequency, and confidence measures cumulated over the working lifetime (cumulative exposure) and the other dividing the cumulative exposure by duration to derive an average level of exposure.

The analysis was carried out in stages. First a screening analysis based on the Mantel-Haenszel (26) approach estimated the odds ratio (OR) between each petroleum-derived liquid and each type of cancer, stratifying on age, ethnic group, socioeconomic status, smoking, and an index of the overall dirtiness of the subject's jobs (ie, blue collar/white collar).

In fact this screening analysis was repeated four times with two different definitions of "exposed" and with two different definitions of the study populations. The cumulative index of exposure was cut at the median to provide a level of exposure that we call "substantial." The basic analysis was carried out once with exposed status defined by any versus none and then by substantial versus none. One set of basic analyses was carried out among all the subjects interviewed, and another set was carried out only among French Canadians, a relatively homogeneous social and genetic grouping that constituted about 60 % of the study population. Any association that appeared to have an elevated odds ratio in any of the four screening runs was earmarked for in-depth analysis.

In-depth logistic regression analyses

First, each association thus selected underwent an analysis to determine which of the hundreds of available covariables might be confounders, and then an analysis to estimate the odds ratio was performed that took these confounders into account. The search for confounders was based on the empirical principle of finding those covariates which, when included as stratification variables, changed the estimate of the disease-exposure odds ratio by more than 10 %. Some established risk factors were included as confounders whether or not they satisfied this criterion. For instance, asbestos, nickel, and chromium were included for any association involving lung cancer.

Using logistic regression methods (2) and including the potential confounders identified, we estimated the disease-exposure odds ratio associated with any level or duration of exposure to the substance, the odds ratio associated with different levels of exposure to the substance, and the odds ratios of subgroups who received their exposure to the substance in different occupations.

Defining the petroleum-derived liquids

The substances selected for analysis in this report are, for the most part, derivatives of petroleum crude oil. They have certain chemical and physical properties in common, and there is considerable overlap in their use patterns. They are all liquid at room temperature. Each substance is a complex mixture with a composition that has varied considerably over time and in different uses. In fact, even within a given era and a given use, the composition of each of these substances can have varied considerably according to such factors as the geographic source of the crude oil, the particular refining process used, and the blending formulation (3). It is conceivable that, within the substance categories we examined, some formulations are dangerous, whereas others are not. Our study could detect risks due to one of the substances only if the most prevalent formulations of the substance were carcinogenic.

Some of the nomenclature used to define these substances is vague and requires clarification. For example, it can be assumed that all those exposed to automotive gasoline in our study population were exposed to leaded gasoline. Those exposed recently may also have had exposure to unleaded gasoline. We made no attempt to identify this subset.

The term "mineral spirits" is used broadly to encompass petroleum-derived solvent mixtures known at various times or in various countries as white spirit, Stoddard solvent, varnish makers' and painters' (VM and P) naphtha, rubber solvent, benzine, and ligroin. Mineral spirits are composed of organic compounds with chain lengths that range from C_5 to C_{12} (25). These hydrocarbons consist mainly of aliphatics (30—90 %), cyclic aliphatics (10—55 %), and aromatics (1—20 %). In the 1970s, concern over the carcinogenicity of benzene led the major petroleum refineries to offer solvent mixtures containing lower concentrations of aromatics of low molecular weight. The aromatic content of these mixtures is now comprised mainly of alkylbenzenes with higher molecular weights.

The compositions of cutting fluids, hydraulic fluids, and lubricating oils have also evolved over time from

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Table 1. Percentage of all the 3 726 subjects exposed to each of 12 petroleum-derived liquids according to degree of exposure.

Substance	Any exposure[a] (%)	High confidence (%)	High frequency (%)	High concentration[b] (%)	>20 years exposure (%)
Automotive gasoline	12.4	10.4	2.3	3.9	4.4
Aviation gasoline	1.3	0.9	0.3	0.5	0.4
Mineral spirits	19.8	14.9	3.1	4.0	9.1
Kerosene	6.3	1.9	0.3	0.8	1.7
Jet fuel	1.2	0.7	0.3	0.4	0.6
Diesel fuel	4.1	2.5	0.6	0.6	1.9
Heating oil	4.6	3.6	1.2	1.0	1.8
Cutting fluids	9.1	5.6	4.5	2.2	3.4
Hydraulic fluids	4.2	2.4	0.6	0.3	1.6
Lubricating oils	31.9	23.8	7.0	3.1	14.0
Other mineral oils	4.1	2.3	1.9	0.4	1.3
Crude oil	0.8	0.5	0.3	0.3	0.3

[a] Exposure attributed with any degree of confidence and at any frequency, concentration, and duration.
[b] Concentration is on a relative scale which is not comparable between substances.

being mainly mineral oil-based to having a variety of formulations, some of which contain little or no mineral oil (eg, emulsified cutting fluids). The term "other mineral oil" is used to cover such diverse oils as rolling oils, heat treating oils, textile oil, penetrating oil, die lubricants, protective coating oils, and oils used in printing ink.

Kerosene is a mixture of petroleum hydrocarbons with carbon chain lengths ranging from 9 to 16 atoms per molecule (30). Its most common uses by our study subjects were as a metal-cleaning solvent, as, for example, among forestry workers who used kerosene to clean and lubricate sawing equipment, and as stove oil, eg, among construction workers in winter. Jet fuels, as coded in this study, include both kerosene and "wide cut" fuels.

Exposure to the combustion products of these substances has not been included in this analysis, but it will be covered in a subsequent report.

Results

Table 1 describes the exposure patterns of our entire study population (3 726 subjects) for each of the 12 petroleum liquids. Lubricating oils was by far the most common exposure; 31.9 % of all subjects were considered to have had potential exposure to lubricating oils in at least one of their jobs. Most of these subjects were considered definitely exposed (23.8 % of the entire sample). However, only 7.0 % of the entire sample had been exposed at a high frequency (more than 30 % of the day) and only 3.1 % were exposed at a high concentration level (on a relative scale). A large number (14.0 %) had over 20 years' exposure to lubricating oils at one level or another of frequency, concentration, and confidence. In contrast, crude oil was the least common, with a lifetime work prevalence of 0.8 % for any level or length of exposure. Table 2 shows the main occupational groups in which exposure occurred for each substance. Most of these substances occurred in many job classes apart from those shown in the table. In addition the indication that a

Table 2. Main occupations for which exposure to each petroleum-derived liquid was attributed in the entire study group of 3 726 subjects.[a]

Substance	N[b]	Main occupations for which exposure to the substance was coded (% of subjects in this occupation)
Automotive gasoline	462	Mechanics and repairmen (24.7 %), sales (mainly service station attendants) (15.4 %), farming (14.3 %), forestry (10.0 %), motor transport (7.4 %)
Aviation gasoline	47	Aircraft mechanics and repairmen (42.6 %)
Mineral spirits	739	Construction trades (especially painters) (20.8 %), mechanics and repairmen (19.6 %), metal machining (5.4 %)
Kerosene	235	Forestry (40.0 %), construction trades (9.4 %), mechanics and repairmen (8.1 %), farming (8.1 %)
Jet fuel	43	Aircraft mechanics and repairmen (27.9 %)
Diesel fuel	154	Mechanics and repairmen (33.8 %), motor transport (9.1 %), excavating and grading (8.4 %)
Heating oil	172	Construction workers (23.3 %), motor transport occupations (19.2 %), stationary engine and utilities operating (17.4 %)
Cutting fluids	338	Metal machining (37.0 %), plumbers and pipefitters (14.2 %), metal shaping (10.1 %), aircraft fabricating (8.0 %)
Hydraulic fluids	155	Mechanics and repairmen (63.9 %), sales (mainly service station attendants) (14.8 %), metal shaping (4.5 %)
Lubricating oils	1189	Mechanics and repairmen (17.2 %), construction trades (9.3 %), metal machining (9.1 %), salesmen of commodities (5.6 %)
Other mineral oils	152	Printing (30.3 %), metal machining and shaping (9.2 %), construction trades (7.9 %), textile and hide processing (7.2 %)
Crude oil	31	Water transport (19.4 %), construction trades (12.9 %), materials handling (9.7 %)

[a] Note that the ordering of occupations does not necessarily reflect the degree of exposure in various occupations. For instance, while the largest occupational category exposed to kerosene was "forestry workers," the exposure level was much lower among forestry workers than among mechanics and repairmen.
[b] This is the number of persons exposed at any level; N is the denominator for each percentage corresponding to the substance in question.

substance was attributed to some workers bearing a given job title does not imply that all workers with that job title were attributed that exposure. For instance, while many of those exposed to hydraulic fluids were

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"mechanics and repairmen" only a fraction of "mechanics and repairmen" were considered to have been exposed to hydraulic fluids. As expected, several of these substances occurred in many of the same occupations.

For each substance coded by our team of chemists, the presumed route of exposure was indicated. For most of the substances in this report, exposure occurred via both respiratory and cutaneous contact. For some of the heavier ones (lubricating oils, hydraulic fluids, other mineral oils) exposure was more often cutaneous than respiratory.

Screening results

Mantel-Haenszel screening analyses were carried out among all the subjects and among the subset of French Canadians. Associations which were elevated among the French Canadians were also elevated in the whole group. We have therefore presented only the results for all the subjects. We estimated the odds ratios between the 12 petroleum-derived liquids and 20 types of cancer. For the rare types of cancer there was a very low power to detect risks; the confidence intervals around the odds ratio estimates were so wide that the findings were not very informative. Tables 3—5 show

Table 3. Odds ratios (OR) between 12 sites of cancer[a] and exposure[b] to automotive gasoline, aviation gasoline, mineral spirits, and kerosene, on the basis of Mantel-Haenszel analyses with five stratifying variables.[c] (N = number of exposed cases, 90 % CI = 90 % confidence interval)

Site	Automotive gasoline			Aviation gasoline			Mineral spirits			Kerosene		
	N	OR	90 % CI	N	OR	90 % CI	N	OR	90 % CI	N	OR	90 % CI
Stomach	44	1.5*	1.2—1.9	3	0.8	0.3—2.7	51	1.0	0.8—1.2	24	1.7*	1.2—2.3
Colon	39	1.0	0.7—1.2	7	1.7	0.7—3.6	57	0.8	0.6—1.0	14	0.7	0.5—1.1
Rectosigmoid	25	0.9	0.7—1.3	3	0.8	0.2—2.7	35	0.7	0.5—0.9	11	0.9	0.5—1.4
Rectum	24	1.1	0.8—1.6	4	2.5	0.6—10.3	42	1.0	0.8—1.3	11	0.9	0.6—1.6
Lung												
Oat cell	26	1.2	0.8—1.6	1	0.4	0.1—3.2	36	1.1	0.8—1.4	0	0.9	0.6—1.5
Squamous cell	53	1.0	0.8—1.3	2	0.4	0.1—1.6	92	1.2	1.0—1.5	34	1.4*	1.0—1.9
Adenocarcinoma	26	1.1	0.8—1.5	2	0.9	0.2—3.8	37	1.0	0.7—1.3	15	1.5	1.0—2.3
Other[d]	19	0.8	0.6—1.1	1	0.4	0.1—3.1	32	0.8	0.6—1.1	13	1.2	0.8—1.9
Prostate	56	1.0	0.8—1.2	6	0.9	0.4—2.0	100	1.3*	1.1—1.5	34	1.1	0.8—1.5
Bladder	64	1.2	0.9—1.4	6	1.0	0.5—2.2	91	1.0	0.8—1.2	31	1.1	0.8—1.5
Kidney	24	1.2	0.8—1.6	7	2.6*	1.2—5.8	39	1.1	0.8—1.4	12	1.3	0.8—2.1
Non-Hodgkin's lymphoma	20	0.8	0.5—1.1	1	0.4	0.1—2.5	35	0.8	0.6—1.1	5	0.4	0.2—0.7

[a] In this table only those site series with over 150 interviewed cases are presented.
[b] Exposure at any level and for any duration.
[c] Stratifying variables: age, socioeconomic status, ethnic group, cigarette smoking, and blue-/white-collar job history.
[d] Includes other and unknown cell types.
* OR was significantly greater than 1.0 at P = 0.05 (one-sided). Note that a lower limit of 1.0 for the 90 % CI does not necessarily imply a significantly elevated OR. The lower limit may have been rounded to 1.0. In addition the test and the confidence interval computations have been based on separate alogorithms (35).

Table 4. Odds ratios (OR) between 12 sites of cancer[a] and exposure[b] to jet fuel, diesel fuel, heating oil, and cutting fluids, on the basis of Mantel-Haenszel analyses with five stratifying variables.[c] (N = number of exposed cases, 90 % CI = 90 % confidence interval)

Site	Jet fuel			Diesel fuel			Heating oil			Cutting fluids		
	N	OR	90 % CI	N	OR	90 % CI	N	OR	90 % CI	N	OR	90 % CI
Stomach	1	0.2	0.0—1.7	10	1.0	0.6—1.6	15	1.4	0.9—2.1	24	1.1	0.8—1.4
Colon	7	2.1	0.9—5.1	10	0.7	0.4—1.1	13	0.9	0.6—1.5	32	1.0	0.8—1.4
Rectosigmoid	2	0.8	0.2—3.8	4	0.4	0.2—0.9	6	0.6	0.3—1.2	20	0.9	0.7—1.3
Rectum	4	2.1	0.6—7.4	11	1.4	0.8—2.5	11	1.5	0.8—2.6	13	0.7	0.4—1.0
Lung												
Oat cell	2	1.3	0.2—7.0	10	1.7	0.9—3.0	13	1.7*	1.0—2.7	23	1.5	1.0—2.1
Squamous cell	1	0.2	0.0—2.4	20	1.5	1.0—2.2	25	1.3	0.9—1.8	39	1.0	0.8—1.3
Adenocarcinoma	2	1.2	0.2—6.6	7	1.0	0.5—1.9	11	1.3	0.8—2.1	19	1.2	0.8—1.7
Other[d]	1	0.6	0.1—6.0	9	1.4	0.8—2.5	5	0.6	0.3—1.1	8	0.4	0.3—0.7
Prostate	4	0.7	0.2—2.1	25	1.7*	1.2—2.5	26	1.4	1.0—1.9	47	1.2	1.0—1.6
Bladder	4	0.7	0.3—1.8	13	0.7	0.5—1.1	18	0.9	0.6—1.3	47	1.2	1.0—1.6
Kidney	7	2.5*	1.1—5.4	10	1.4	0.8—2.3	8	1.1	0.6—2.1	16	1.0	0.7—1.5
Non-Hodgkin's lymphoma	2	0.7	0.2—3.2	10	1.1	0.7—1.8	6	0.7	0.4—1.3	22	1.3	0.9—1.8

[a] In this table only those site series with over 150 interviewed cases are presented.
[b] Exposure at any level and for any duration.
[c] Stratifying variables: age, socioeconomic status, ethnic group, cigarette smoking, and blue-/white-collar job history.
[d] Includes other and unknown cell types.
* OR was significantly greater than 1.0 at P = 0.05 (one-sided). Note that a lower limit of 1.0 for the 90 % CI does not necessarily imply a significantly elevated OR. The lower limit may have been rounded to 1.0. In addition the test and the confidence interval computations have been based on separate alogorithms (35).

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Table 5. Odds ratios (OR) between 12 sites of cancer[a] and exposure[b] to hydraulic fluids, lubricating oils (and greases), other mineral oils and crude oil, on the basis of Mantel-Haenszel analyses with five stratifying variables.[c] (N = number of exposed cases, 90 % CI = 90 % confidence interval)

Site	Hydraulic fluids			Lubricating oils			Other mineral oils			Crude oil		
	N	OR	90 % CI	N	OR	90 % CI	N	OR	90 % CI	N	OR	90 % CI
Stomach	18	1.9*	1.3—2.8	80	0.9	0.8—1.1	7	0.6	0.3—1.1	3	1.4	0.4—5.0
Colon	15	1.1	0.7—1.6	105	0.9	0.8—1.1	16	1.1	0.7—1.6	3	1.5	0.3—6.8
Rectosigmoid	8	0.8	0.4—1.4	70	0.9	0.7—1.1	4	0.4	0.2—0.9	0	0	N.A.
Rectum	8	1.0	0.5—1.9	61	1.0	0.8—1.2	6	0.6	0.3—1.3	5	5.8*	1.1—29.9
Lung												
Oat cell	8	0.9	0.5—1.7	54	1.0	0.7—1.3	6	1.0	0.5—2.0	1	0.7	0.1—8.0
Squamous cell	15	0.7	0.5—1.1	143	1.2	1.0—1.4	10	0.7	0.4—1.2	7	2.8*	1.0—7.6
Adenocarcinoma	6	0.6	0.3—1.1	54	0.9	0.7—1.2	10	1.7	1.0—3.2	1	0.8	0.1—9.7
Other[d]	10	1.1	0.7—1.9	50	0.8	0.6—1.0	12	1.8*	1.0—2.9	0	0	N.A.
Prostate	24	1.5	1.0—2.2	166	1.3*	1.1—1.5	22	1.4	1.0—2.1	6	2.3	0.7—7.1
Bladder	17	0.9	0.6—1.2	149	1.0	0.9—1.2	24	1.3	0.9—1.9	1	0.2	0.1—2.0
Kidney	9	1.1	0.6—2.0	63	1.2	0.9—1.5	9	1.3	0.7—2.2	2	1.2	0.2—6.3
Non-Hodgkin's lymphoma	7	0.8	0.4—1.4	59	0.9	0.7—1.1	7	0.9	0.5—1.6	1	0.5	0.1—3.8

[a] In this table only those site series with over 150 interviewed cases are presented.
[b] Exposure at any level and for any duration.
[c] Stratifying variables: age, socioeconomic status, ethnic group, cigarette smoking, and blue-/white-collar job history.
[d] Includes other and unknown cell types.
* OR was significantly greater than 1.0 at P = 0.05 (one-sided). Note that a lower limit of 1.0 for the 90 % CI does not necessarily imply a significantly elevated OR. The lower limit may have been rounded to 1.0. In addition the test and the confidence interval computations have been based on separate alogorithms (35).

the screening results for the 12 substances by the 12 cancer types which had over 150 cases and thus reasonable statistical power. These tables are based on any exposure versus no exposure. Twelve associations were significantly elevated (P < 0.05, one-sided), and all of the 12 were selected for in-depth analysis. We also carried out the corresponding set of screening analyses with exposure defined by substantial exposure versus none. Although we have not shown these results because of space limitations, we did select any association which was significant in these results for in-depth analysis. Six more associations were thereby selected [diesel fuel-rectum cancer, diesel fuel-lung (squamous cell) cancer, heating oil-rectum cancer, cutting fluids-lung (oat cell) cancer, cutting fluids-non-Hodgkin's lymphoma, other mineral oil-bladder cancer]. In addition, among the rarer cancer types omitted from tables 3—5, there was only one statistically significant association based on five or more exposed cases, that between Hodgkin's lymphoma and mineral spirits exposure. Finally, we also selected for in-depth analysis three associations which were of borderline statistical significance, which hinted at higher risk among the substantially exposed, and which were of interest because of other work. The cutting fluids-bladder cancer association had been reported in the literature (39). The lung (squamous cell) cancer-lubricating oils association largely involved an occupation (mechanics and repairmen) which had been reported to be at risk for lung cancer (12). The lung (squamous cell) cancer-mineral spirits association was of interest because one of the main occupational groups exposed to mineral spirits (namely, painters) had been reported to be at risk for lung cancer (12).

A total of 22 associations were thereby selected, three with stomach cancer, three with rectal cancer, seven with various histological types of lung cancer, three with prostate cancer, two each with bladder and kidney cancer, and one each with Hodgkin's and non-Hodgkin's lymphoma.

In-depth analyses

Each selected association was analyzed with the purpose of obtaining odds ratio estimates for various exposure subgroups, adjusted for all potential confounders. First a series of analyses was carried out to identify a short list of potential confounders. Then, using logistic regression, we estimated odds ratios for various exposure subgroups. The results for all 22 associations are shown in table 6.

We estimated risk associated with any level or duration of exposure, as well as that associated with subgroups at different levels of exposure. When an association was based on 20 or more exposed cases, we categorized them into four exposure subgroups, based on the level and duration of exposure. We have called the groups short-low, short-high, long-low, long-high. When there were fewer than 20 exposed cases, we categorized them into two exposure subgroups, based on cumulative exposure (which combines level and duration). These we have called nonsubstantial and substantial.

Concerning the occupation-specific odds ratios, it should be noted that "exposed" is defined as exposed to the substance of interest in the occupation in question and "unexposed" is defined as not exposed to the substance regardless of whether or not the subject worked in the occupation of interest. For each association, we examined the risk in up to six of the main occupations in which the exposure occurred. However

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Table 6. Detailed analyses of selected associations[a] between the 12 petroleum-derived liquids and cancer types, the substances being subdivided according to exposure level and the occupation in which the exposure occurred.

Exposure subgroup[a]	N[b]	OR$_1$[c]	OR$_2$[d]	90 % CI[e]
Automotive gasoline-stomach cancer				
Exposure level[f]				
Short-low	6	1.1	1.2	0.6—2.4
Short-high	6	0.9	0.9	0.4—1.9
Long-low	21	1.9	2.0	1.3—3.1
Long-high	11	2.2	2.3	1.2—4.2
All combined	44	1.5	1.6	1.1—2.3
Occupation[g]				
Mechanics & repairmen	14	1.9	2.0	1.1—3.5
All others	30	1.4	1.5	1.0—2.2
Aviation gasoline-kidney cancer				
Exposure level[f]				
Nonsubstantial	1	1.8	1.5	0.3—8.6
Substantial	6	3.9	3.9	1.7—8.8
Both combined	7	2.9	3.1	1.5—6.5
Mineral spirits-squamous-cell lung cancer				
Exposure level[f]				
Short-low	9	1.0	1.0	0.5—2.0
Short-high	11	1.1	1.2	0.6—2.1
Long-low	28	1.1	1.1	0.7—1.6
Long-high	44	1.6	1.7	1.2—2.3
All combined	92	1.3	1.3	1.0—1.7
Occupation[g]				
Janitors	7	2.4	2.3	1.0—5.5
Metal machinists	5	2.0	1.9	0.8—4.8
All others	80	1.2	1.2	0.9—1.6
Mineral spirits-prostate cancer				
Exposure level[f]				
Short-low	8	1.0	0.9	0.4—1.8
Short-high	18	1.6	1.7	1.1—2.8
Long-low	31	1.0	1.0	0.7—1.4
Long-high	43	1.8	1.8	1.3—2.6
All combined	100	1.3	1.3	1.1—1.7
Mineral spirits-Hodgkin's lymphoma				
Exposure level[f]				
Nonsubstantial	4	1.1	1.0	0.4—2.6
Substantial	12	2.8	2.0	1.0—4.1
Both combined	16	2.1	1.6	0.8—3.0
Kerosene-stomach cancer				
Exposure level[f]				
Nonsubstantial	20	2.0	2.0	1.3—3.0
Substantial	4	1.0	1.0	0.4—2.5
Both combined	24	1.7	1.7	1.2—2.5
Occupation[g]				
Forestry	15	3.0	2.8	1.7—4.7
All others	9	1.0	1.0	0.6—1.9
Jet fuel-kidney cancer				
Exposure level[f]				
Nonsubstantial	1	1.7	2.1	0.3—12.7
Substantial	6	3.4	3.4	1.5—7.6
Both combined	7	3.0	3.1	1.5—6.6
Diesel fuel-rectum cancer				
Exposure level[f]				
Nonsubstantial	3	0.6	0.5	0.1—1.7
Substantial	8	2.4	1.6	0.7—3.9
Both combined	11	1.3	1.0	0.5—2.0
Diesel fuel-squamous-cell lung cancer				
Exposure level[f]				
Nonsubstantial	7	0.9	1.0	0.4—2.0
Substantial	13	2.6	2.5	1.3—4.7
Both combined	20	1.6	1.6	1.0—2.6
Occupation[g]				
Mechanics & repairmen	8	2.0	2.0	0.9—4.2
All others	12	1.5	1.4	0.8—2.6
Diesel-fuel-prostate cancer				
Exposure level[f]				
Nonsubstantial	17	2.4	2.3	1.3—4.0
Substantial	8	1.4	1.4	0.7—2.9
Both combined	25	1.9	1.9	1.2—3.0
Heating oil-rectum cancer				
Exposure level[f]				
Nonsubstantial	3	0.7	0.3	0.1—1.7
Substantial	8	2.6	2.6	1.2—5.5
Both combined	11	1.5	1.4	0.7—2.7
Heating oil-oat-cell lung cancer				
Exposure level[f]				
Nonsubstantial	6	1.9	1.6	1.0—4.2
Substantial	7	1.8	1.7	1.1—4.2
Both combined	13	1.9	1.7	1.2—3.4
Cutting fluids-bladder cancer				
Exposure level[f]				
Short-low	10	0.9	0.9	0.5—1.6
Short-high	10	1.4	1.4	0.8—2.6
Long-low	12	1.3	1.3	0.8—2.3
Long-high	15	1.6	1.5	0.9—2.6
All combined	47	1.3	1.3	0.9—1.7
Occupation[g]				
Metal machinists	21	1.5	1.5	1.0—2.2
Plumbers & pipefitters	8	1.8	1.9	1.0—3.8
All others	18	0.9	0.9	0.6—1.4
Cutting fluids-oat-cell lung cancer				
Exposure level[f]				
Nonsubstantial	10	1.4	1.0	0.5—2.1
Substantial	13	1.6	1.6	0.8—3.1
Both combined	23	1.5	1.3	0.7—2.2
Cutting fluids-non-Hodgkin's lymphoma				
Exposure level[f]				
Nonsubstantial	9	1.0	0.8	0.4—1.5
Substantial	13	1.9	1.8	1.0—3.1
Both combined	22	1.4	1.2	0.8—1.8
Hydraulic fluids-stomach cancer				
Exposure level[f]				
Nonsubstantial	15	2.3	2.2	1.3—3.6
Substantial	3	0.9	1.0	0.4—2.8
Both combined	18	1.9	1.8	1.2—2.9
Lubricating oils-squamous-cell lung cancer				
Exposure level[f]				
Short-low	19	1.2	1.3	0.8—2.1
Short-high	25	1.0	1.0	0.7—1.6
Long-low	44	1.6	1.6	1.1—2.3
Long-high	55	1.2	1.2	0.9—1.6
All combined	143	1.2	1.3	1.0—1.6
Lubricating oils-prostate cancer				
Exposure level[f]				
Short-low	23	1.2	1.1	0.7—1.8
Short-high	28	1.4	1.2	0.8—2.0
Long-low	59	1.2	1.0	0.7—1.4
Long-high	56	1.5	1.2	0.8—1.7
All combined	166	1.3	1.1	0.9—1.4
Occupation[g]				
Farmers	13	1.5	1.5	0.8—2.6
Mechanics & repairmen	38	2.0	1.6	1.1—2.3
All others	115	1.2	1.0	0.8—1.2
Other mineral oils-other lung cancer				
Exposure level[f]				
Nonsubstantial	5	1.1	1.2	0.5—2.8
Substantial	7	3.7	4.2	1.8—10.0
Both combined	12	1.9	2.0	1.1—3.7

(continued)

(continued)

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Table 6. Continued.

Exposure subgroup [a]	N [b]	OR$_1$ [c]	OR$_2$ [d]	90 % CI [e]
Other mineral oils-bladder cancer				
Exposure level [f]				
Nonsubstantial	13	1.2	1.2	0.7—2.1
Substantial	11	1.7	1.7	0.9—3.2
Both combined	24	1.4	1.4	0.9—2.1
Crude oil-rectum cancer				
Exposure level [f]				
Nonsubstantial	2	6.2	4.6	0.6—35.3
Substantial	3	4.3	3.4	1.0—11.7
Both combined	5	4.8	3.7	1.3—10.6
Crude oil-squamous-cell lung cancer				
Exposure level [f]				
Nonsubstantial	3	3.4	3.1	0.9—11.0
Substantial	4	3.5	3.9	1.2—12.3
Both combined	7	3.5	3.5	1.5—8.2

[a] These are the associations which were significant in at least one of the two screening runs and which had at least five exposed cases. A few associations which were of borderline significance were also selected.

[b] N = number of exposed cases.

[c] The odds ratio (OR$_1$) estimates for each association are based on a logistic regression model including the following five a priori covariates: age, ethnic group, socioeconomic status, smoking, job "dirtiness."

[d] The odds ratio (OR$_2$) estimates for each association are based on a logistic regression model including all potential confounders identified in the confounder searching procedure described in the Methods section, except for other petroleum-derived liquids examined in this paper. For each substance, it is implicitly assumed that unexposed men have an OR of 1.0. For each association, the referents consisted of other types of cancer as indicated in reference 35.

[e] 90 % confidence interval for OR$_2$.

[f] Exposure level was divided into two or four categories depending on whether there were fewer or more than 30 exposed cases. When the total number was less than 30, the level of exposure was defined by the cumulative exposure index used in the Mantel-Haenszel analyses and dichotomized at the same point along the scale of that index to provide two categories which have been called nonsubstantial and substantial. When the total number exceeded 30, four categories were defined by dichotomizing the duration of exposure and dichotomizing the degree of exposure. Short- and long-term exposure was defined by a 10-year cut point. Low and high exposure was defined by the median of the distribution of values of the index comprising the following characteristics of the exposure: concentration, frequency, and the chemists' confidence that the exposure occurred. See reference 35 for a description of index E, used in the two-category definition, and index A, used in the four-category definition.

[g] Occupation refers to the occupation in which the subject was exposed to the substance in question. Selected for presentation were one or two occupations in which the odds ratio differed from the overall odds ratio. If the odds ratios were constant across the main occupations in which the substance was found, no occupations were listed. Each man was classified into only one occupation category; if he was exposed to the substance in two different occupations, the job of longest duration was used. Thus the sum of the numbers across occupations is the same as that across exposure levels, and it equals the total number of men with this site of cancer and exposure to this substance. Note that the odds ratios corresponding to each occupation refer to the risk for those men in the occupation who have been exposed to the substance of interest, not for all men in the occupation. The level of exposure was ignored in these occupation-substance analyses.

in table 6 we present only those occupations in which the risk was particularly high.

The data-based potential confounders were divided into the following three categories: nonoccupational covariates (eg, beverage consumption, marital status), other occupational exposures than other petroleum-derived liquids, and other petroleum-derived liquids. Each model was built up gradually in five cumulative steps. First, we estimated the crude odds ratio. Second, we included the same a priori confounders that were included in the Mantel-Haenszel analyses, though the continuous variables among them were included as continuous variables. Then we included in sequence each of the three aforementioned categories of the

data-based confounders. It was not clear-cut which of these steps provided the most "valid" odds ratio estimate (5). Space limitation mitigates against presenting all five, and in any event the variation in the odds ratio estimates across steps was generally minor, especially across the last three steps. We decided to present the estimates from two models, ie, that based on a priori confounders only and that based on all variables except other petroleum-derived liquids. If the results from the full model differed from the latter, it is mentioned in the text and its meaning discussed.

For each association there was a distinct regression model containing from 5 to 25 covariates, depending on which covariables were earmarked in the data-based search for confounders. While there may be some interest in showing which variables went into the respective models, in fact it is not important for the interpretation of the disease-exposure odds ratios because we have "controlled" for all variables in our data set, either by confirming in the initial step that their inclusion in the model did not affect the odds ratio estimate or by including them in the regression model. Because it would take considerable space to present them all, we have chosen not to present the covariables included in each model.

Discussion

There were many significant findings, some undoubtedly by chance and some possibly because of real cause-and-effect relations. While acknowledging the possibility of false positive results, we must also note the possibility of false negatives. As implied by the width of the confidence intervals in tables 3—5, the power to detect risks was only moderate for most of the associations analyzed. The power may have been further compromised because of a misclassification error in the exposure assessment. Furthermore the strategy of employing other cancer patients as referents for each case series was a "conservative" strategy, possibly leading to some attenuation of risk estimates. Finally the inclusion of data-based confounders in the models may also be a conservative strategy. On the one hand, including more variables than is strictly necessary increases the variability of estimates. On the other, it may also introduce some overadjustment.

We recognize the arbitrary and limited nature of statistical significance as a criterion for selecting associations for in-depth analysis. Nevertheless, for our purpose, we believe it is as useful an arbitrary criterion as any other. The main objective of the in-depth analysis was to try to separate the false positives from the true positives. In this process we used criteria such as the stability of statistical significance once the confounders were included in the model, the strength of association, dose-response, and coherence with experimental or other epidemiologic information. Unfortunately, there have been very few other epidemiologic

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studies bearing directly on the carcinogenicity of any of these substances. The available evidence, such as it is, derives indirectly from studies of occupational or industrial groups who may have been exposed to the substance in question. Most of these studies were based on the occupations mentioned on the death certificates or tumor registers. Such evidence suffers from several deficiencies — notably, the poor validity of the occupational information, its questionable appropriateness as a surrogate for specific substances, the questionable validity of the attributed cause of death as an indicator of cancer incidence, and the lack of information on potential confounding factors (34).

When odds ratios are discussed without qualification, it is assumed that we are referring to the more fully adjusted odds ratio in table 6, namely, that designated as OR_2.

Automotive and aviation gasoline

We found an association between automotive gasoline exposure and stomach cancer. The odds ratio was 2.0 among exposed mechanics and repairmen, compared to 1.5 among other exposed workers. Although only a minority of mechanics were attributed exposure to automotive gasoline, they were often exposed at relatively high levels because they used it regularly as a degreasing agent. We carried out an analysis of selected job titles in our data set and found that all mechanics had an odds ratio of 1.3 for stomach cancer, in contrast with the odds ratio of 2.0 for the subgroup exposed to automotive gasoline. The stomach cancer-automotive gasoline association was significant with evidence of a dose-response relationship. Even when other petroleum liquids (kerosene, hydraulic fluids) were added to the model, the odds ratios for automotive gasoline did not decrease.

There have been no other epidemiologic studies directly providing evidence on stomach cancer risks from automotive gasoline exposure. Leaded automotive gasoline has usually been formulated with two lead-scavenger additives, dichloroethane (ethylene dichloride) and dibromoethane (ethylene dibromide). Both compounds are mutagens and induce tumors of the forestomach in rats and mice after oral administration (31). Ethylene dichloride has produced tumors in a spectrum of other organs, while topical administration of ethylene dibromide to mice has resulted in skin tumors (31). Both compounds can be absorbed percutaneously. The stomach cancer-automotive gasoline association is compatible with the carcinogenic action of one or both of these additives, possibly aided by percutaneous absorption.

Insofar as there has been suspicion of human carcinogenicity from exposure to automotive gasoline, the evidence has pointed to a risk for kidney cancer. While the epidemiologic evidence for kidney cancer risk has been inconclusive (11, 14, 27, 32, 42), exposure to unleaded automotive gasoline has been associated with renal cancer in rats (24). Although the slight excess risk of kidney cancer among workers exposed to automotive gasoline (OR = 1.2) was not statistically significant, we did find a significant cluster of seven kidney cancer patients with exposure to aviation gasoline. Six of them were also exposed to jet fuel, which was also associated with kidney cancer. Because of the high correlation between aviation gasoline and jet fuel, it was difficult to disentangle the effects on kidney cancer. When both were included in a regression model, the odds ratio for jet fuel decreased somewhat, while that for aviation gasoline was unaffected. This result hints at a greater role for aviation gasoline than for jet fuel. Aviation gasoline differs in composition from leaded automotive gasoline by its high content of alkylate naphthas, constituted mainly of branched alkanes (9). These compounds are strongly suspected of being responsible for the animal nephrotoxicity of various petroleum products (17). It has furthermore been hypothesized that there may be a causal relation between nephrotoxic changes and the appearance of renal neoplasms in rats exposed to unleaded automotive gasoline (24). It is thus tempting to hypothesize a link between exposure to highly branched alkanes and renal cancer. This link could explain the animal carcinogenicity of unleaded automotive gasoline, which is known to contain about 20 % alkylate stream (24), and the present finding of excess kidney cancer due to aviation gasoline, since aviation gasoline also contains a high proportion of alkylate stream (50—70 %) (9). Thus our finding of a kidney cancer-aviation gasoline association is important because it suggests a possible association between kidney cancer and unleaded automotive gasoline.

Mineral spirits

Exposure to mineral spirits was significantly associated with squamous-cell lung cancer, especially among those with long-high exposure. The risks were particularly elevated in small clusters of metal machinists and janitors. Although not shown in table 6, there was also some excess lung cancer among construction workers exposed to mineral spirits, many of whom were painters (OR = 1.4). In fact the janitors received their exposure to mineral spirits through painting activities. In the analyses of job titles, the entire groups of metal machinists and construction workers had odds ratios of less than 1.0 for squamous-cell lung cancer. This finding implies that exposure to mineral spirits is an important factor. Several studies have reported excess lung cancer risk among painters (12, 13, 28, 29, 37). In Dubrow & Wegman's (12) synthesis of several large studies involving standardized mortality ratios and proportionate mortality ratios, the aggregate standardized mortality ratio for lung cancer among painters was 140 (12). At least one case-referent study also found a large excess of lung cancer among painters, especially among those who did not wear protective equipment (37). The possible etiologic role of mineral spirits has not previously been addressed, but seems to us to be realistic.

Both prostate cancer and Hodgkin's lymphoma showed signs of association with mineral spirits. The evidence in our data was stronger in the case of prostate cancer than for Hodgkin's lymphoma, although the biological plausibility of such an association is not self-evident.

Kerosene and jet fuels

Although the screening analyses turned up an association between kerosene and stomach cancer, the evidence from the in-depth analyses was not persuasive. The association was entirely attributable to a stomach cancer risk among forestry workers. The level of exposure to kerosene among forestry workers was generally low. The odds ratio for stomach cancer among the entire group of forestry workers was as high as that among the subset exposed to kerosene. A significant excess risk for stomach cancer among forestry workers has also been reported in a large proportionate mortality ratio (PMR) study carried out in the state of Washington in the United States (PMR = 115) (29).

The jet fuel-kidney cancer association has already been mentioned. It is interesting to note further that nephrotoxic effects have been reported in male rats exposed to various kinds of military jet fuels, including wide cut and kerosene base types similar to the ones coded in our study (25). Exposure to synthetic jet fuels, associated with the development of kidney cancers in male rats in the same study, was not, however, judged to be present in our study population.

Based on small numbers, a nonsignificant excess of colorectal cancers was found among the workers exposed to jet fuel (table 4). In Washington State, which contains a large aircraft industry, there was a slight excess of colorectal cancer among aircraft mechanics (22 observed, 18 expected) (29).

Diesel fuel and heating oil

Diesel fuel and heating oil are similar in composition. In the screening analyses and in the in-depth logistic regressions, there was a significant association between diesel fuel and squamous-cell lung cancer. Furthermore, although they were not significant, there were excesses both for oat-cell and for "other" lung cancer cell types in relation to diesel fuel. We therefore carried out a separate set of analyses combining all types of lung cancer except adenocarcinomas. The odds ratio corresponding to OR_2 in table 6 for "any" exposure was 1.6 (90 % confidence interval 1.1---2.4, N = 39). The odds ratios corresponding to the four subcategories short-low, short-high, long-low, and long-high were 1.9, 2.0, 1.1, and 2.0, respectively. These results support the hypothesis of a risk for nonadenocarcinoma lung cancer due to diesel fuel. There was also a significant odds ratio between heating fuel and oat-cell lung cancer. Because of the similarity between heating and diesel fuel, this finding may also be thought to support the lung cancer-diesel fuel hypothesis. Al-

though there has been some previous evidence of an association between diesel exhaust and lung cancer (19), there has been little evidence of direct relevance to the liquid itself. Nevertheless exposure to the liquid and to the exhaust products undoubtedly has some elements in common.

The association between diesel fuel and prostate cancer was also significant in the logistic regression, but there was, if anything, an inverse dose-response relationship. Finally both of these substances were associated with rectal cancer. After logistic regression, both associations were reduced, though both maintained a hint of dose-response. The numbers were small and the confidence intervals wide.

Hydraulic fluids

Hydraulic fluids comprise a chemically heterogeneous class of substances with very little epidemiologic or experimental evidence. Automobile mechanics who were exposed to transmission and brake fluids constituted the main group in this category. The level of exposure of most mechanics to these substances was rather low. Only stomach cancer was significantly associated with hydraulic fluids in the Mantel-Haenszel screening runs. While the odds ratio estimate shown in table 6 was significant, it was not persuasive for two reasons. First, the risk was elevated only for those workers with the lowest exposure. Second, when gasoline exposure was added as a confounder to the regression model, the odds ratios decreased and were no longer significant.

Lubricating oils

Lubricating oils is one of the most commonly used classes of substances in the industrial environment. They are used in all kinds of occupations and industries and would include both used and unused oils. The overall association with prostate cancer which turned up in the screening analyses virtually disappeared in the in-depth analysis. There remained excesses of prostate cancer among farmers and mechanics exposed to lubricating oils, who together comprised less than one-third of all workers with exposure to lubricating oils. We carried out analyses within each of these two subgroups to determine if in either case there was a dose-response relation between level of lubricating oil exposure and prostate cancer risk. There was none. The excess of prostate cancer among farmers is consistent with the results presented in several reports (6, 12, 33). The reasons remain obscure. It is not clear whether the apparent excess among mechanics and repairmen exposed to lubricating oils reflects a risk from these substances or from some other factor. On the basis of small numbers, Wen et al (43) found a "nonsignificant" standardized mortality ratio of 182 for prostate cancer among oil refinery workers involved in the processing of lubricating oil. Vena et al (38) found no excess prostate cancer in an auto engine and parts

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manufacturing complex, where again there was presumed exposure to lubricating oils, though this finding too was based on small numbers.

In our data, lubricating oils were also associated with squamous-cell lung cancer. Although the OR_2 was only 1.3, it was based on large numbers and was of borderline statistical significance. There was no clear dose-response relation. Dubrow & Wegman (12), in their synthesis of national studies involving standardized mortality ratios (SMR) and proportionate mortality ratios, concluded that lung cancer risks are high for mechanics (aggregate SMR = 122). Most workers with this job title are exposed to lubricating oils. There have been a number of historic cohort studies among workers with probable exposure to lubricating oils. Two found proportionate mortality ratios in excess of 100 for lung cancer (16, 38), while others did not (4, 43). However, none of these studies was large or convincing. In sum, there is some suggestion of an increased risk of both lung and prostate cancer, though the evidence is not persuasive for either site. If there is a risk for lung cancer, it may be limited to squamous-cell tumors.

Cutting fluids and other mineral oils

The categories of cutting fluids and other mineral oils have had varying formulations over the years and also

Table 7. Brief summary (by site of cancer) of the strength of evidence for each association selected for the in-depth analysis.

Association	Strength of evidence [a]	
	Statis-tical [b]	Dose-response [c]
Stomach cancer-automotive gasoline [d]	+ +	+ +
Stomach cancer-kerosene	+ +	− −
Stomach cancer-hydraulic fluids	+ +	− −
Rectum cancer-diesel fuel	−	+
Rectum cancer-heating oil	−	+ +
Rectum cancer-crude oil	+ +	−
Lung (oat cell) cancer-heating oil	+ +	+
Lung (oat cell) cancer-cutting fluids	−	+
Lung (squamous cell) cancer-mineral spirits [e]	+	+ +
Lung (squamous cell) cancer-diesel fuel [e]	+	+ +
Lung (squamous cell) cancer-lubricating oils	+	−
Lung (squamous-cell) cancer-crude oil	+ +	+
Lung (other) cancer-other mineral oils	+	+ +
Prostate cancer-mineral spirits	+ +	+ +
Prostate cancer-diesel fuel	+ +	− −
Prostate cancer-lubricating oils [e]	−	−
Bladder cancer-cutting fluids [e]	+	+
Bladder cancer-other mineral oils [e]	+	+
Kidney cancer-aviation gasoline [d]	+ +	+ +
Kidney cancer-jet fuel [d]	+ +	+ +
Non-Hodgkin's lymphoma-cutting fluids	−	+
Hodgkin's lymphoma-mineral spirits	+	+

[a] + + = moderate to strong evidence of excess risk, + = weak evidence of excess risk, − = no evidence of excess risk, − − = evidence against the hypothesis of excess risk (eg, inverse dose-response).
[b] Based on the results of the logistic regression for "any" exposure. It takes into account the magnitude of the odds ratio, its statistical significance, and the number on which it is based.
[c] Refers to the trend among subgroups at different levels and/or durations of exposure and to the odds ratio in the highest exposure subgroup.
[d] Some experimental evidence which supports this association is presented in the text.
[e] Some previous epidemiologic evidence which supports this association is presented in the text. For the bladder-cutting oil association that evidence was considerable; for the other associations, the evidence was indirect and weak.

different uses. Both were associated with bladder cancer. Though these associations were of borderline significance, the odds ratios were greatest in the respective long-high exposure categories. The bladder cancer risk was somewhat higher among machinists and plumbers exposed to cutting fluids than among other workers with the same exposure.

There were associations between cutting fluids and oat-cell lung cancer and non-Hodgkin's lymphomas which were no longer significant after the adjustment for confounders. An association between "other mineral oils" and "other lung cancer" was barely significant and was based on small numbers.

Aside from the well-documented association of cutting fluids with cancer of the scrotum (41) and skin cancer (21), there has been less conclusive evidence concerning the effects of these substances on the sites of cancer included in our study. Several studies have reported excess bladder cancer risks in occupational groups with presumed exposure to cutting fluids (1, 7, 8, 18, 36, 38, 40), while only one investigation found no such excess (10). Some studies have reported excess lung cancer (8, 38), while others have not (10, 22). Some have reported excess stomach cancer risk (10, 22), while others have not (38). The studies providing data on stomach and lung cancer were based on small numbers and cannot be considered persuasive. Our findings are clearly negative for stomach cancer and fairly negative for lung cancer, but suggestive for bladder cancer. In the past, some cutting oils have been formulated with aromatic amines, a class of compounds which includes known human bladder carcinogens (20, 39). Also, N-nitrosamines, a class of animal carcinogens, have been detected in cutting fluids (23). Given the prior evidence from other epidemiologic studies and the fact that cutting oils have in the past been formulated with known carcinogens, the fact that both cutting fluids and other mineral oils should have turned up in our study as more strongly associated with bladder cancer than with any other cancer lends credibility to these associations.

Crude oil

Crude oil was apparently associated with rectal and squamous-cell lung cancers, but these associations were based on very small numbers. One of the main groups in which this exposure occurred, namely, seamen, would likely have had very different life-styles than the rest of our study population.

General comments

While we presented and discussed the associations under the headings of the various substances, some readers may be interested to see them grouped by cancer site. In addition it is useful to summarize briefly the evidence presented. Table 7 presents an admittedly rough summary of the evidence from our study on each association that was examined in-depth.

Our purpose was to generate hypotheses. In our view the most promising leads to follow-up from our results are the following: (i) the effects of exposure to leaded automotive gasoline on the occurrence of stomach cancer, (ii) the effects of exposure to aviation gasoline on the occurrence of kidney cancer and the possible implications of this finding for a similar association for unleaded automotive gasoline, (iii) the effects of exposure to mineral spirits on the occurrence of squamous-cell cancer of the lung, (iv) the effects of exposure to diesel fuel on the occurrence of nonadenocarcinoma lung cancer, (v) the effects of exposure to lubricating oil on the occurrence of squamous-cell lung cancer, (vi) the effects of exposure to cutting oils and other mineral oils on the occurrence of bladder cancer, (vii) the effects of exposure to mineral spirits and diesel fuel on the occurrence of prostate cancer.

Some of the hypotheses suggested will be followed up in our own data set with additional analyses regarding latency, interactions with smoking and other factors, effect modification, and more complex regression models. Such analyses were beyond the scope of this initial paper.

References

1. Anthony HM, Thomas GM. Tumors of the urinary bladder: An analysis of the occupations of 1,030 patients in Leeds, England. J Natl Cancer Inst 45 (1970) 879—895.
2. Baker RJ, Nelder JA. The GLIM system: Release 3. Generalised linear interactive modelling. Royal Statistical Society, Oxford 1978.
3. Bingham E, Trosset RP, Warshawsky D. Carcinogenic potential of petroleum hydrocarbons: A critical review of the literature. J Environ Path Toxicol 3 (1980) 483—563.
4. Bond GB, Flores GH, Shellenberger RJ, Cartmill JB, Fishbeck WA, Cook RR. Nested case-control study of lung cancer among chemical workers. Am J Epidemiol 124 (1986) 53—66.
5. Breslow NE, Day N. The analysis of case-control studies. In: Davis W, ed. Statistical methods in cancer research. International Agency for Research on Cancer, Lyon 1982. (IARC scientific publications no 32).
6. Burmeister LF. Cancer mortality in Iowa farmers, 1971—78. J Natl Cancer Inst 66 (1981) 461—464.
7. Cartwright R. Occupational bladder cancer and cigarette smoking in West Yorkshire. Scand J Work Environ Health 8 (1982): suppl 1, 79—82.
8. Coggon D, Panett B, Acheson ED. Use of job exposure matrix in an occupational analysis of lung and bladder cancers on the basis of death certificates. J Natl Cancer Inst 72 (1984) 61—65.
9. CONCAWE Special Task Force on Safe Use of Petroleum Fuels. Health aspects of petroleum fuels — Potential hazards and precautions for individual classes of fuels. CONCAWE Publications, The Hague 1985. (Report no 85/51).
10. Decoufle P. Further analysis of cancer mortality patterns among workers exposed to cutting oil mists. J Natl Cancer Inst 61 (1978) 1025—1030.
11. Domiano SF, Vena JE, Swanson MK. Gasoline exposure, smoking and kidney cancer. J Occup Med 27 (1985) 398—399.
12. Dubrow R, Wegman D. Setting priorities for occupational cancer research and control-synthesis of the results of occupational disease surveillance studies. J Natl Cancer Inst 71 (1983) 1123—1142.
13. Dubrow R, Wegman DH. Cancer and occupation in Massachussetts: A death certificate study. Am J Ind Med 6 (1984) 207—230.
14. Enterline PE, Viren J. Epidemiologic evidence for an association between gasoline and kidney cancer. Environ Health Perspect 62 (1985) 303—312.
15. Gérin M, Siemiatycki J, Kemper H, Bégin D. Obtaining occupational exposure histories in epidemiologic case-control studies. J Occup Med 27 (1985) 420—426.
16. Greenberg M. A proportional mortality study of a group of newspaper workers. Br J Ind Med 29 (1972) 15—20.

17. Halder CA, Warne TM, Hatoum NS. Renal toxicity of gasoline and related petroleum naphthas in male rats. Adv Mod Environ Toxicol 7 (1984) 73—88.
18. Howe GR, Burch JD, Miller AB, Cook GM, Esteve J, Morrison B, Gordon P, Chambers LW, Fodor G, Winsor GM. Tobacco use, occupation, coffee, various nutrients and bladder cancer. J Natl Cancer Inst 64 (1980): 4, 701—713.
19. Howe GR, Fraser D, Lindsay J, Presnal B, Zhang Yu S. Cancer mortality (1965—77) in relation to diesel fume and coal exposure in a cohort of retired railway workers. J Natl Cancer Inst 70 (1983): 6, 1015—1019.
20. International Agency for Research on Cancer. Polynuclear aromatic hydrocarbons: Part 2. Carbon blacks, mineral oils (lubricant base oils and derived products) and some nitroarenes. Lyon 1984. (IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, volume 33).
21. Jarvholm B, Fast K, Lavenius B, Tomsic P. Exposure to cutting oils and its relation to skin tumors and premalignant skin lesions on the hands and forearms. Scand J Work Environ Health 11 (1985) 365—369.
22. Jarvholm B, Lillienberg L, Sallsten G, Thiringer G, Axelson O. Cancer morbidity among men exposed to oil mist in the metal industry. J Occup Med 23 (1981) 333—337.
23. Keefer LK, Hansen TJ. Primary amine use and other strategies for preventing human exposure to N-nitroso compounds: Application to cutting fluids. In: Bartsch H, O'Neill IK, Castegnaro M, Okada M; ed. N-nitroso compounds: Occurrence and biological effects. International Agency for Research on Cancer, Lyon 1982. (IARC scientific publications no 41).
24. MacFarland HN, Ulrich CE, Holdsworth CE, Kitchen DN, Halliwell WH, Blum SC. A chronic inhalation study with unleaded gasoline vapor. J Am Coll Toxicol 3 (1984) 231—248.
25. MacNaughton MG, Uddin DE. Toxicology of mixed distillate and high energy synthetic fuels. Adv Mod Environ Toxicol 7 (1984) 121—132.
26. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22 (1959) 719—748.
27. McLaughlin JK, Blot WJ, Mehl ES, Stewart MS, Venable FS, Fraumeni JF. Petroleum-related employment and renal cell cancer. J Occup Med 27 (1985) 672—674.
28. Menck HR, Henderson BE. Occupational differences in rates of lung cancer. J Occup Med 18 (1976) 797—801.
29. Milham S Jr. Proportionate mortality ratios in Washington State: By cause of death and occupation 1950—1971. Department of Health, Education and Welfare, Washington, DC 1976. (DHEW publication no NIOSH 76—175A).
30. National Institute for Occupational Safety and Health. Occupational exposure to refined petroleum solvents. US Government Printing Office, Washington, DC 1977. (DHEW (NIOSH) publication no 77—192).
31. National Toxicology Program, Public Information Office. National toxicology program, third annual report on carcinogens. US Department of Health and Human Services, Research Triangle Park, NC 1983. (PB-83-135855).
32. Raabe GK. Kidney cancer epidemiology in petroleum related studies. Adv Mod Environ Toxicol 7 (1984) 259—271.
33. Saftlas AF, Blair A, Cantor KP, Hanrahan L, Anderson HA. Cancer and other causes of death among Wisconsin farmers. Am J Ind Med 11 (1987) 119—129.
34. Siemiatycki J, Day N, Fabry J, Cooper JA. Discovering carcinogens in the occupational environment: A novel epidemiologic approach. J Natl Cancer Inst 66 (1981) 217—225.
35. Siemiatycki J, Wacholder S, Richardson L, Dewar R, Gérin M. Discovering carcinogens in the occupational environment: Methods of data collection and analysis of a large case-referent monitoring system. Scand J Work Environ Health 13 (1987) 486—492.
36. Silverman DT, Hoover RN, Albert S, Graff KM. Occupation and cancer of the lower urinary tract in Detroit. J Natl Cancer Inst 70 (1983) 237—245.
37. Stockwell HG, Matanoski GM. A case-control study of lung cancer in painters. J Occup Med 27 (1985) 125—126.
38. Vena JE, Sultz HA, Fielder RC, Barnes RE. Mortality of workers in an automobile engine and parts manufacturing complex. Br J Ind Med 42 (1985) 85—93.
39. Vineis P, Di Prima S. Cutting oils and bladder cancer. Scand J Work Environ Health 9 (1983) 449—450.
40. Vineis P, Magnani C. Bladder cancer and occupation in males: A case-control study. Int J Cancer 35 (1985) 599—607.
41. Waldron HA. A brief history of scrotal cancer. Br J Ind Med 40 (1983) 390—401.
42. Wen CP, Tsai SP, Moffitt KB, Bondy M, Gibson RL. Epidemiologic studies of the role of gasoline (hydrocarbon) exposure in kidney cancer risk. Adv Mod Environ Toxicol 7 (1984) 245—258.
43. Wen CP, Tsai SP, Weiss NS, Gibson RL, Wong O, McClellan WA. Long-term mortality study of oil refinery workers: IV Exposure to the lubricating-dewaxing process. J Natl Cancer Inst 74 (1985) 11—18.

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